## AMENDMENTS TO THE DRAWINGS

The attached five sheets of drawings include Figures 1-4B. The spelling of the word "Figure" has been corrected on each of the five sheets. Annotated copies are attached showing the correction and a set of Replacement Sheets (5 sheets) is also attached.

Attachments: Annotated Sheets (5)

Replacement Sheets (5)

## REMARKS

The Office Action of December 31, 2003 has been reviewed and the Examiner's comments carefully considered. The present Amendment amends claims 11, 13, 14 and 21 in accordance with the originally-filed specification, and cancels claim 28. Claims 11-27, 29 and 30 remain in this application.

Initially, the Examiner has objected to the drawings as containing a grammatical error. Specifically, the Examiner notes that the word "Figure" is misspelled in all of Figs. 1-4B. All of these figures have been modified, and the spelling of "Figure" has been corrected accordingly. Withdrawal of this objection to the drawings is respectfully requested.

Next, the Examiner objects to the specification as containing language that is unclear and indefinite. Specifically, in the Summary of the Invention section of the present application, the Examiner notes that the sentence directed to "the problem of this invention" is not clear. Applicants agree, and the paragraph under this section has been modified accordingly, and now indicates "the object" of the invention. With respect to the expression "classifying infrared spectra," the Examiner believes that such a phrase is not clear and not explained in the specification. Applicants respectfully draw the Examiner's attention to page 10, lines 16-22, which details the classification process. In particular, the method classifies a spectrum based upon a two-class problem as being either healthy or TSE-infected. In view of the above explanation and the foregoing amendments, Applicants respectfully request withdrawal of the objection to the specification.

Claim 11 stands objected to for containing abbreviations, which should be accompanied by full names. Specifically, independent claim 11 contains the abbreviations "TSE" and "BSE." These abbreviations have been fully defined in amended claim 11. In addition, the Examiner has suggested modifying the expression "that the spectral

characteristics...are recorded" to "and recording the spectral characteristics." Applicants have fully adopted the Examiner's suggested modifications and amended claim 11 accordingly. Finally, the Examiner objects to claims 13 and 14 as reciting wrong wavenumbers. These claims have been modified according to the Examiner's suggestions through the foregoing amendment. Therefore, in view of these amendments, withdrawal of the objections to claims 11, 13 and 14 is respectfully requested. Claim 28 is objected to under 37 C.F.R. § 1.75 as being substantially duplicative of claim 14. Therefore, the Examiner has issued a double patenting rejection, since these two claims cover the same thing. Applicants agree, and claim 28 has been canceled by the foregoing amendment.

Claims 11-30 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, with respect to claim 11, the Examiner believes that the method is unclear since it is directed to diagnosing TSE-induced pathologic changes, but also indicates the sample is *apriori* TSE-changed. Accordingly, the Examiner suggests that if Applicants wished to express that infrared radiation is directed to any tissue sample showing pathological changes, with no preliminary knowledge of the cause of the pathology, the word "TSE" should be removed from the language of step (a). Applicants are in agreement with the Examiner and have modified independent claim 11 to adopt the Examiner's suggested modifications. In addition, with respect to claim 21, the Examiner has rejected this claim since the phrase "the human organs" lacks antecedent basis. Again, the Examiner's suggested modifications, with respect to modifying the dependency of claim 21, have been fully adopted. Claim 21 now depends from dependent claim 12, as opposed to independent claim 11. In view of these claim modifications, and the adoption of the Examiner's suggested changes, withdrawal of the Section 112, second paragraph, indefiniteness rejections is respectfully requested.

Substantively, claims 11-15, 17-21 and 24-30 stand rejected under 35 U.S.C. § 103(a) as being obvious over Caughey et al., "Secondary Structure Analysis of the Scrapie-Associated Protein PrP 27-30 in Water by Infrared Spectroscopy", Biochemistry, Vol. 30, No. 31, pp. 7672-7680, May 1991 (hereinafter "the Caughey reference"), in view of Choo et al., "In Situ Characterization of β-Amyloid in Alzheimer's Diseased Tissue by Synchrotron Fourier Transform Infrared Microspectroscopy", Biophysical Journal, Vol. 71, pp. 1672-1679, 1996 (hereinafter "the Choo 1996 reference"). Further, claims 16, 22 and 23 stand rejected under 35 U.S.C. § 103(a) as being obvious over the Caughey reference in view of the Choo 1996 reference and in further view of Choo et al., "Infrared Spectra of Human Central Nervous System Tissue: Diagnosis of Alzheimer's Disease by Multivariate Analyses," Biospecroscopy, Abstract, 1995 (hereinafter "the Choo 1995 reference"). In view of the foregoing amendments and the following remarks, Applicants respectfully request withdrawal of these rejections.

Independent claim 11 of the present application, as amended, is directed to a method for diagnosing transmissible spongiform encephalopathies-induced (TSE-induced) pathological changes in tissues. These changes are caused by scrapie, bovine spongiform encephalopathies (BSE) or other similar diseases of the TSE group of diseases. The method includes the steps of: (a) directing infrared radiation onto a tissue sample and recording the spectral characteristics after interaction with the sample; (b) comparing the infrared spectrum thus obtained against a reference database that contains infrared spectra of TSE-infected and non-infected tissue; and (c) classifying the infrared spectrum as a spectrum obtained from TSE infected or non-infected tissues.

The Caughey reference is directed to the study of the secondary structure of the proteinase K resistant core of PrP-res (PrP-res 27-30) using Fourier transform infrared spectroscopy. Prior to performing the infrared spectroscopy, this reference teaches preparing

highly purified PrP-res 27-30 by digesting a homogenisat of hamster brain with proteinase K followed by centrifugation and washing steps (see Chapter "PrP-res 27-30 Purification" under "Materials and Methods"). Next, the Caughey reference discloses the production of a fine suspension of PrP-res 27-30 immediately before performing the infrared spectroscopy.

The Choo 1996 reference discloses a method that uses a Fourier transform infrared microspectroscopic technique to select areas of interest for spectral measurement and to mask regions of potential contamination. *"In so doing, it is possible to obtain infrared spectra only of β-amyloid and not the surrounding grey matter within it lies"* (see Abstract; emphasis added). Using conventional infrared microscopy *"[t]issue sections were viewed with light microscope objectives to identify areas of interest, and infrared spectra were then recorded..."* (see p. 1673, right col. lines 6-8; emphasis added). Furthermore, on page 1674, left col., second paragraph, it is confirmed that with conventional infrared microspectroscopy *"undesirable tissue areas can be masked and specific areas of interest in the tissue can be investigated"*. Also with synchrotron infrared microspectroscopy, spectra were obtained only from a rectangular region of tissue outline in Fig. 3 *"chosen for mapping because of the presence of a dense amorphous deposit that was suspected to be a neuritic plaque (labelled NP?) within the grey matter (G)"* (see page 1675, left column, last paragraph and Fig. 3).

The present invention, and independent claim 11 of the present application, are distinguishable from the Caughey reference, the Choo 1996 reference, and the Choo 1995 reference in several aspects. First, the inventors of the invention of the present application have used either small pieces of brains (Example 1), homogenized tissue materials (Example 2), or cryostat sections of samples (Example 3) for the infrared spectroscopy. However, the method of the present invention does not teach or suggest the use of any purified or otherwise chemically or biomechanically-modified materials. In addition, the Examiner has admitted that the Caughey

reference does not teach the direct infrared irradiation of tissue samples. The Examiner believes that the Choo 1996 reference teaches direct infrared irradiation. However, the Choo 1996 reference teaches only the use of infrared microspectroscopy for selected areas which contain a dense amorphous deposit. In this manner, infrared spectra are obtained from the β-amyloid only, but are not obtained from the surrounding grey area. However, the present invention provides a novel and non-obvious method that uses direct irradiation to identify TSE-induced pathological changes in tissues. Importantly, such TSE-induced pathological changes were identified by infrared radiation without a prior selection of an area suspected to contain pathological changes. Such a modified method provides unexpected results and is clearly not obvious in view of the teachings of the Choo 1996 reference. It should be noted that the method of the present invention does not detect known amyloid proteins, such as prions and A-beta proteins, instead detecting other as of yet uncharacterized pathological changes in the tissue, which surprisingly correlate with the detection of TSE. This is yet another novel and unexpected result of the presently-claimed method.

Independent claim 11 of the present application, as amended, is directed to a method for diagnosing TSE-induced pathological changes in tissues. Independent claim 11 specifically identifies that infrared radiation is directed onto the tissue sample, without a prior selection of a suspected area. Accordingly, the Caughey reference and the Choo 1996 reference, whether used alone or in combination, do not teach or suggest the method as claimed in the present application, which directly irradiates a tissue sample without prior selection of a suspected area.

It is noted that the Examiner has used the Choo 1996 reference to cure the deficiencies of the Caughey reference by demonstrating the combination of the methods. As set forth in MPEP, § 2143.03, to establish *prima facie* obviousness of a claimed invention, all of the

claim limitations must be taught or suggested by the prior art. Further, the Examiner cannot use the claims as a blueprint for locating separate claim elements in separate prior art references without considering the teachings of the prior art as a whole and without considering the complete teachings of the separate references. There is nothing in the Caughey reference and the Choo 1996 reference that suggests the desirability of their combined teachings. Specifically, there is no motivation for a person skilled in the art to perform infrared spectroscopy with tissue without any pre-selection of the area to be investigated. In addition, transmissible spongiform encephalopathies (TSEs) are a different disease than Alzheimer's disease and have much different characteristics. For example, contrary to TSE, Alzheimer's disease is consistently accompanied by pronounced neuro-inflammatory processes, which are caused by tau and A-beta proteins. Furthermore, again other than for TSEs, a great number of pathologically upregulated cerebral mediators of host defense have been identified in Alzheimer's disease, which, while possibly underlaying the findings of the Choo 1995 reference, do not underlay the findings of the present invention. There is no incentive to combine these references together in order to arrive at the claimed subject matter of the present application. In the absence of some "clear and particular" motivation to combine the teachings of the cited prior art, the rejection is improper. Winner Int'l Royalty Corp. v Wang, 202 F.3d 1340, 1348-49 (Fed. Cir. 2000).

For the foregoing reasons, independent claim 11 is not anticipated by or rendered obvious over the Caughey reference, the Choo 1996 reference, the Choo 1995 reference or any of the prior art of record, whether used alone or in combination. There is no hint or suggestion in any of the references cited by the Examiner to combine these references in a manner which would render the invention, as claimed, obvious. Reconsideration of the rejection of independent claim 11, as amended, is respectfully requested.

Claims 12-27, 29 and 30 depend either directly or indirectly from and add further limitations to independent claim 11 and are believed to be allowable for the reasons discussed hereinabove in connection with independent claim 11. Therefore, for all the above reasons, reconsideration of the rejections of claims 12-27, 29 and 30 is respectfully requested.

Applicants respectfully draw the Examiner's attention to the granted European Patent Office patent, which is directed to identical subject matter as originally claimed. Specifically, the originally-claimed subject matter may be found in granted European Patent No. 1 181 552 B1. For all the foregoing reasons, Applicants believe that claims 11-27, 29 and 30, as amended, are patentable over the cited prior art and in condition for allowance. Reconsideration of the rejections and allowance of all pending claims 11-27, 29 and 30 are respectfully requested.

Respectfully submitted,

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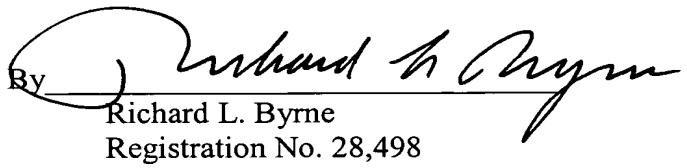
By 

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